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10/817,644	04/02/2004	Brian Hashemi	BDT-0003	2841

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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,644	HASHEMI, BRIAN	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-134* is/are pending in the application.

4a) Of the above claim(s) *106-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *79-134* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/18/04; 10/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 79-105, with traverse, filed September 6, 2007 is acknowledged and has been entered. Claims 106-134 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Currently, claims 79-134 are pending. Claims 79-105 are under examination.

2. Applicant traverses the restriction requirement on the grounds that there is no serious burden established in examining both Groups I and II, encompassing a diagnostic method and a method of monitoring, given their level of relatedness. Applicant specifically argues that a search on the claimed method for disease diagnosis will reveal art relevant to the claimed method for disease monitoring.

In response, Applicant's argument is not persuasive because, albeit related, diagnostic methods are functionally and structurally distinct from methods of monitoring a disease with respect to steps of determining an indication and the nature of the standards used. Accordingly, literature search for each method is distinct since the structural requirements of each invention are different. While searches would be expected to overlap, there is no reason to expect the searches to be coextensive.

Specification

3. A reference to the prior application has been inserted in the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76). However, the status of the prior application ASN 10/407,262, i.e. US Patent Number or abandoned, is missing.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 79-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 79 is ambiguous in reciting, "labeling at least one cell type from the mixture" and then "assessing the content of cytoskeletal protein associated with at least two cell types" because it is unclear how the cytoskeletal protein content of at least two specific cell types can be obtained when only [at least] one of the cell types from the mixture is being labeled. Additionally, the term "associated" is a subjective term that lacks a comparative basis for defining its metes and bounds. How are the cytoskeletal proteins associated with the cell, i.e. contained in the cell (intracellularly) or released from the cell type? See also claims 80, 84, 86, and 94 which recite "associated with."

Claim 79 is indefinite in being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the

necessary structural connections. See MPEP § 2172.01. In this case, it is unclear how the cytoskeletal content should correlate to the presence or absence of a disease state. Should the presence , absence, increase, or decrease or the content provide indication of the presence or absence of the disease state. See also claims 80, 84, 86, and 94 which recite "associated with."

Claim 87 is objected to in reciting, "the at least two comprise". Perhaps, Applicant intends, "the at least two cell types comprise."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 79-81, 83, 85-90, 92-94, 96-101, 104, and 105 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Direct Measurement of Neutrophil F-actin Content in Microvolume Whole Blood Samples, International Archives of Allergy and Immunology, 110: 325-331 (1996)).

Chen et al. teach a method for assessing the presence or absence of bacterial infection (neonatal sepsis) in neonatal subjects using whole blood samples (Abstract and page 331). In practice, microvolume (100 ul) whole blood samples comprising a mixture of cells having a plurality of cell types are stabilized (fixed) using FACS Lysing

solution to fix the leucocytes. Therefrom, F-actin, a cytoskeletal protein contained within the cells is further labeled using NBD phallacidin (F-actin probe) so as to allow flow cytometric measurement and quantification, the F-actin level or concentration of which is correlated to the bacterial infection. Chen et al. al teach that prior to stabilizing the cells in the sample, N-formyl-Met-Leu-Phe or FMLP (biologically active agent/stimulant/chemoattractant), is added to the mixture of cells which results to dose dependent increase in F-actin content in at least two cell types of neutrophils present in whole blood or isolated neutrophils from the whole blood. Chen et al. indeed teach that in alternative known methods whereupon neutrophils are isolated from other cells, the neutrophils are incubated with FMLP at 37°C, i.e. physiological temperature, fixed using formaldehyde, and labeled with NBD phallacidin in a single step in a single step (Abstract; p. 325, col. 1; and p. 326, col. 1). At least two leucocytic/neutrophilic cell types expressing CD45 and CD14 (i.e. cell surface antigens) from the mixture are labeled using FITC-labeled anti-CD45 and PE-labeled CD14 (cell-type specific reagents) and then analyzed for size (forward angle scatter) and granularity (side angle scatter) using flow cytometry (FACScan) (p. 326. col. 2 and Figure 2). Chen et al. also provide performing the same method for measuring F-actin content on two other cell types: lymphocytes and monocytes (p. 328, col. 2). Chen et al. also teach comparing F-actin content in response to FMLP stimulation in at least two cell types of neutrophils (segmented and band) between Twin B cyanotic subject and Twin A "normal" control sample and also normal adults (p. 326, col. 2 to p. 327, col. 1; p. 328, col. 2; and Figure 7). In as far as claims 97, 98 and 104, bacterial infections are known to be caused by

bacteria (bioagent), toxins (chemical agent), and cytokine (immune modulator) (Abstract and p. 331). The whole blood sample is collected from a subject into a tube containing non-chelating anticoagulant (EDTA) (p. 326, col. 1). Chen et al. provide that by using whole blood samples, F-actin polymerization after FMLP stimulation shows two subpopulations of neutrophils noted at 30 seconds after stimulation whereupon a majority of the neutrophils were stimulated to a higher level of F-actin content, but some neutrophils remained in the area of lower F-actin content. The F-actin content at 300 seconds however, became homogeneous (p. 327, col. 2 and p. 330, cols. 1 and 2). Accordingly, it is deemed that Chen et al. anticipates the claimed invention.

6. Claims 79, 81-83, 87-90, 93, 94, 96, 99, 100, 104, and 105 are rejected under 35 U.S.C. 102(a) as being anticipated by Pillar et al. (A Facile, reproducible, species-independent whole blood procedure for measuring leucocyte actin polymerization response to chemoattractants, ISAC XXI International Congress, My 4-9, 2002, San Diego California) (Abstract).

Pillar et al. teach a method for assessing the presence or absence of chemotaxis (disease state) in subjects using whole blood samples. In practice, the whole blood samples comprising a mixture of cells having a plurality of cell types, i.e. leucocytes, are stabilized (fixed) using formaldehyde and FACS Lysing solution. Therefrom, F-actin (actin polymerization) contained within the cells is further labeled using phalloidin or phallacidin (F-actin probe) so as to allow measurement and quantification of the protein. Pillar et al. al teach that prior to stabilizing the cells in the sample, a plurality of

biologically active agents or chemoattractants including LTB4, FMLP, eotaxin, SDF1a, and PGD2 are added to the mixture of cells which results to variations in responses of leucocyte populations or cell types. Pillar et al. provide that a benefit of the method is that it allows measurement and examination of response of more than one cell type to various chemoattractants in a single reaction volume. See entire Abstract.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (International Archives of Allergy and Immunology, 110: 325-331 (1996)) in view of Pillar et al. (ISAC XXI International Congress, My 4-9, 2002, San Diego California).

Chen et al. is discussed supra. Chen et al. differ from the instant invention in failing to teach correlating the content of the F-actin protein contained in at least two cell types exposed to a plurality of bioactive agents with that of a control.

Pillar et al. is discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to correlate the F-actin values obtained in the method of Pillar which assesses chemotaxis from different bioactive agents, with F-actin levels obtained from normal controls such as taught in the method of Chen because Chen specifically taught

correlating F-actin patient results to normal control to assess neonatal sepsis. One of ordinary skill in the art at the time of the instant invention would have been motivated to correlate the F-actin results obtained by Pillar to normal F-actin control or reference values as taught in the method of Chen because running control or reference standards is part of standard laboratory procedure for purposes of determining accuracy of immunological assay procedures or assessing the presence or absence of disease states in diagnostic methods.

8. Claims 95 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (International Archives of Allergy and Immunology, 110: 325-331 (1996)) or Pillar et al. (ISAC XXI International Congress, My 4-9, 2002, San Diego California) in view of Wheeler et al. (Influenza A Virus Alters Structural and Biochemical Functions of the Neutrophil Cytoskeleton (Journal of Leucocyte Biology 47: 332-343 (1990)).

Chen et al. and Pillar et al. are discussed supra. Chen et al. and Pillar et al. differ from the instant invention in failing to teach determining the presence or absence of F-actin using microscopy so as to assess viral infection.

Wheeler et al. provide that Influenza A Virus alters chemotactic, oxidative, and secretory functions of polymorphonucleated leucocytes (PMNs) and that cytoskeletal proteins such as F-actin play a role in these processes (Abstract). Wheeler et al. then teach that viral infection can be assessed, by determining the level of F-actin in PMNs using flow cytometry or immunofluorescent microscopy. In practice, PMNs comprising a

plurality of cell types are stabilized (fixed) using formalin. Therefrom, F-actin contained within the cells is further labeled using NBD-phallacidin (F-actin probe) so as to allow measurement and quantification of the protein (p. 333, cols. 1 and 2). Wheeler et al. teach that FMLP is added to the sample prior to stabilizing the cells in the sample (Abstract). Wheeler et al. correlate the level of F-actin measured to the presence of exposure to Influenza A Virus.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to assess viral infection using F-actin in the method of Wheeler using the method taught by Chen or Pillar, because Chen and Pillar taught that disease states such as bacterial infection or chemotaxis can be assessed by flow cytometrically detecting F-actin values on specifically labeled leucocyte cells present in whole blood samples whereas Wheeler also found application and correlation of F-actin levels to assessing other disease states which involve actin polymerization such as in viral diseases.

9. Claim 91 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (International Archives of Allergy and Immunology, 110: 325-331 (1996)) or Pillar et al. (ISAC XXI International Congress, My 4-9, 2002, San Diego California) in view of Connelly et al. (US 5,422,277).

Chen et al. and Pillar et al. are discussed supra. Chen et al. and Pillar et al. differ from the instant invention in failing to teach that the sample is stabilized by fixation at a temperature of about 27°C to about 50°C.

Connelly et al. disclose various fixatives used to fix cells without destroying cellular properties. Connelly et al. specifically teach fixing cells from a whole blood sample with a fixative composition comprising phosphate buffer solution, DMSO, DNBS, polyethylene sorbitans monolaurate or monooleate (TWEEN 20 or TWEEN 80), and formaldehyde (see column 9, lines 10-14) and then incubating the cell mixture with the fixative composition for 20 minutes to 2 hours at temperatures ranging from 0°C to 37°C (see column 9, lines 20-48). Connelly et al. disclose collecting the whole blood sample into heparin anticoagulant containing tube (see Example 1). In column 8, lines 31-40, Connelly et al. provide use of saponin as detergent for incorporation into the fixative composition.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Connelly in adjusting the temperature parameter requirement during fixation to a temperature of 27°C to 37°C, into the method of determining F-actin content in whole blood sample as taught by Chen or Pillar, because Chen specifically taught fixing, permeabilizing, and staining isolated neutrophils in a single step by adding phosphate-buffered formaldehyde, incubating the mixture at 37°C for 10 minutes, and then detecting the cells for the presence and amount of F-actin and Connelly specifically taught that whole blood samples can be fixed at temperatures of 0°C to 37°C; hence, absent evidence to the contrary, it would have been obvious to one of ordinary skill in the art to optimize whole blood sample methods as taught by Chen and Pillar using temperature requirements that appear to

work more accurately on other sample types as suggested by Connelly, because optimization of procedural requirements, is standard laboratory practice.

10. Claim 103 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (International Archives of Allergy and Immunology, 110: 325-331 (1996)) or Pillar et al. (ISAC XXI International Congress, My 4-9, 2002, San Diego California) in view of Egger et al. (A simple method for measuring the F-actin content of human polymorphonuclear leucocytes in whole blood, Virchows Arch 438: 394-397 (2001)).

Chen et al. and Pillar et al. are discussed supra. Chen et al. and Pillar et al. differ from the instant invention in failing to teach assessing cancer.

Egger et al. teach measuring F-actin in polymorphonuclear leucocytes (PMNs) present in whole blood containing a mixture of cells including PMNs or neutrophils, lymphocytes, and monocytes (Abstract and Figure 1) whereupon heparinized whole blood sample is fixed with glycerol (lysis reagent) and formaldehyde in phosphate buffer at a selected temperature for 15 minutes (p. 395, col. 1). Thereafter, Eggers et al. teach labeling the F-actin cytoskeleton using FITC-labeled phalloidin (F-actin probe) and determining the F-actin content of each subpopulation of PMN leucocytes using FACSCAN and then correlating the F-actin result to the presence of inflammatory disease state or cancer (tumor necrosis induction) (p. 395, col. 2 and p. 396, col. 2). The light scatter diagrams of each of the leucocyte subpopulations are shown in Figure 1. Eggers et al. teach statistically comparing quantitation values for F-actin between the

FMLP-stimulated samples and blank samples (p. 395, col. 1, p. 396, cols. 1 and 2, and Figure 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to assess cancer using F-actin in the method of Egger using the methods taught by Chen or Pillar because Chen and Pillar taught that disease states such as bacterial infection or chemotaxis can be assessed by flow cytometrically detecting F-actin values on specifically labeled leucocyte cells present in whole blood samples whereas Egger also taught application and correlation of F-actin levels to assessing other disease states which involve actin polymerization such as inflammatory disease state and cancer.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

July 3, 2008